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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re: | Patent Application of<br>Patrick Trotter *et al.* | :<br>: | Attorney Docket No.:<br>**101713-5027** |
| Appln. No.: | **10/529,127** | : | Examiner: Ronald T. Niebauer |
| Filed: | October 13, 2005 | : | Confirmation No.: 6570 |
| For: | ENZYME-SENSITIVE<br>THERAPEUTIC WOUND DRESSINGS | : | Group Art Unit: 1654 |

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**REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR § 1.114**

**RESPONSE AFTER FINAL OFFICE ACTION**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In response to the Final Office Action dated March 12, 2010, the period for response to which has been extended by two months to August 12, 2010, by the Petition for Two-Month Extension of Time and fee payment transmitted herewith, Applicants hereby respond as follows. This Response is being filed in conjunction with a Request for Continued Examination.

## AMENDMENTS

**Listing of Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A wound dressing comprising:

I) a liquid permeable wound contacting layer;

II) an intermediate layer; and

III) an outer, liquid-impervious backing layer;

wherein at least one of said wound contacting and intermediate layers comprise:

(a) a donor layer comprised of a therapeutic agent; and

(b) a barrier layer, said barrier layer comprising a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a protease associated with wound fluid such that the rate of release of the therapeutic agent increases in the presence of the protease, wherein the protease is associated with wound infection or ulcer formation, further wherein said protease selected from the group consisting of proteases that are elevated during infection and proteases that are elevated in wounds that are apparently not clinically infected but which go on to become infected within a few days, wherein the barrier layer initially separates the donor layer in the wound dressing from wound fluid when in use.

2. (Canceled)

3. (Currently amended) A wound dressing according to claim 1 wherein the polymers themselves are not degraded by the ~~protease or other factors~~ proteases that may be present in the wound environment.

4. (Previously presented) A wound dressing according to claim 1 wherein the polymer is a synthetic polymer.

5. (Original) A wound dressing according to claim 4 wherein the polymer is a polymer of N- (2-hydroxypropyl) methyacrylamide (HPMA).

6. (Currently amended) A wound dressing according to claim 1 wherein the oligopeptidic sequences comprise a sequence in the range of 3 to 15 amino acids in length.

7. (Withdrawn) A wound dressing according to claim 1, wherein the protease is elastase and wherein the oligopeptidic sequence comprises or consists of lys-gly-ala-ala-ala-lys **(SEQ ID NO: 1)**, -Ala-Ala-Ala-, Ala-Ala-Pro-Val **(SEQ ID NO: 2)**, Ala-Ala-Pro-Leu **(SEQ ID NO: 3)**, Ala-Ala-Pro-Phe **(SEQ ID NO: 4)**, Ala-Ala-Pro-Ala **(SEQ ID NO: 5)** or Ala-Tyr-Leu-Val **(SEQ ID NO: 6)**.

8. (Withdrawn) A wound dressing according to claim 1, wherein the protease is a matrix metalloproteinase and wherein the oligopeptidic sequence comprises or consists of-Gly-Pro-Y-Gly-Pro-Z- **(SEQ ID NO: 7)**,-Gly-Pro-Leu-Gly-Pro-Z- **(SEQ ID NO: 8)**,-Gly-Pro- Ile-Gly-Pro-Z- **(SEQ ID NO: 9)**, or-Ala-Pro-Gly-Leu-Z- **(SEQ ID NO: 10)**, where Y and Z are amino acids.

9. (Withdrawn) A wound dressing according to claim 1, wherein the protease is a collagenase and wherein the oligopeptidic sequence comprises or consists of-Pro-Leu-Gly-Pro-D-Arg-Z- **(SEQ ID NO: 11)**,-ProLeu-Gly-Leu-Leu-Gly-Z- **(SEQ ID NO: 12)**,-Pro-Gln-Gly- lle-Ala-Gly-Trp- **(SEQ ID NO: 13)**,-Pro-Leu-Gly-Cys (Me)-His- **(SEQ ID NO: 14)**,-Pro-Leu-Gly-Leu-Trp-Ala- **(SEQ ID NO: 15)**,-Pro-Leu-Ala-Leu-Trp-Ala-Arg- **(SEQ ID NO: 16)**, or-Pro-Leu-Ala-Tyr-Trp-Ala-Arg- **(SEQ ID NO: 17)**, where Z is an amino acid.

10. (Withdrawn) A wound dressing according to claim 1, wherein the protease is a gelatinase and wherein the oligopeptidic sequence comprises or consists

11. (Currently amended) A wound dressing according to claim 1 wherein the protease is thrombin and wherein the oligopeptidic sequence comprises or consists of Gly-Arg-Gly-

Asp **(SEQ ID NO: 19)**, Gly-Gly-Arg[[-]], [[-]]Gly-Arg-Gly-Asp-Asn-Pro **(SEQ ID NO: 20)**, Gly-Arg- Gly-Asp-Ser **(SEQ ID NO: 21)**, Gly-Arg-Gly-Asp-Ser-Pro-Lys **(SEQ ID NO: 22).**

12. (Withdrawn) A wound dressing according to claim 1, wherein the protease is stromelysin and wherein the oligopeptidic sequence comprises or consists of-Pro-TyrAla-Tyr-Trp-Met-Arg- **(SEQ ID NO: 23)**.

13. (Previously presented) A wound dressing according to claim 1 wherein the therapeutic agent is an antimicrobial agent, a pain relieving agent, an antiseptic, an analgesic, a local anaesthetic, or a protease inhibitor.

14. (Previously presented) A wound dressing according to claim 1 wherein the therapeutic agent is incorporated within the matrix.

15. (Previously presented) A wound dressing according to claim 14 wherein the wound contacting layer of the dressing comprises the matrix within which the therapeutic agent is incorporated.

16. (Previously presented) A wound dressing according to claim 14 wherein the intermediate layer comprises the matrix within which the therapeutic agent is incorporated.

17. (Canceled)

18. (Currently amended) A wound dressing according to claim 1 wherein the barrier layer comprises a sheet comprising apertures; wherein ~~the apertures are substantially blocked~~ substantially the whole area of the apertures in the apertured sheet is blocked by the matrix before exposure to wound fluid.

19. (Previously presented) A wound dressing according to claim 1, wherein the donor layer is provided behind the barrier layer.

20. (Canceled)

21. (Canceled)

22. (Currently amended) A wound dressing according to claim 1 wherein the wound dressing further comprises at least one ~~additional~~ absorbent layer.

23. (Canceled).

## REMARKS

The Office Action mailed on March 12, 2010, has been reviewed and the comments of the Examiner carefully considered. Claims 1, 3-6, 11, 13-16, 18, 19 and 22 are pending and under examination. Claims 1, 3, 6, 11, 18 and 22 have been amended. Support for these amendments may be found in the specification. No new matter is believed to have been added by way of these amendments.

### Claim Objections

The Examiner objected to claim 11 for the use of a dash ("-") immediately preceding and immediately following the amino acid sequences listed in the claim. Applicants have amended claim 11 herein to remove the extra dashes, as recommended by the Examiner.

Applicants submit that, in view of the amendments to the claim 11 made herein, the Claim Objection has been overcome.

### Rejections under 35 U.S.C. § 112, Second Paragraph ("Indefiniteness")

The Examiner rejected various claims as allegedly being indefinite for the reasons set forth below.

1. Claims 1, 3-6, 13-16, 18, 19 and 22 were rejected as allegedly indefinite for recitation of the phrase "protease associated with wound infection or ulcer formation". Applicants respectfully disagree. While not in agreement with the rejection, but in an attempt to advance prosecution, Applicants have amended claim 1, from which the remaining rejected claims depend, to recite that the claimed proteases are selected from the group consisting of proteases that are elevated during infection and proteases that are elevated in wounds that are apparently not clinically infected but *which go on to become infected within a few days*.

Applicants submit that there is abundant support for this claim language throughout the specification, and for example, at lines 4-8 on page 4 of the specification, as well as pages 1-3 of the specification. As set forth in the specification, signs and indications of clinical infection (i.e., signs and indications making clinical infection "apparent") include, but are not limited to,

chemical signs of infection, such as redness or pain. The absence of such signs makes it "apparent" that there is no clinical infection.

As set forth in the specification on page 2, at lines 16-26, the claimed invention includes the discovery that wound fluid from wounds that are apparently not clinically infected but which go on to become infected within a few days have elevated levels of neutrophil elastase activity and may also have high levels of other inflammatory enzymes, such as macrophage proteases, other neutrophil proteases, bacterial collagenase, plasmin, hyaluronidase, kallikrein or t-PA. Further, chronic wounds, such as venous ulcers, pressure sores and diabetic ulcers have a disordered wound-healing metabolism even in the absence of infection. In particular, wound chronicity is associated with elevated levels of protease enzymes in the wound that interfere with the normal processes of tissue formation and destruction in the wound. Therefore, the absence of such signs makes it "apparent" that there is no clinical infection.

The specification directly supports the claim amendments, and provides guidance to the skilled artisan as to what falls within the scope of the claim.

2. Claims 1, 3-6, 13-16, 18, 19 and 22 were also rejected as allegedly indefinite for recitation of the term "apparently not clinically infected." Applicants respectfully submit that the entire specification provides sufficient guidance to define this term, and for example, the text on pages 1 and 2 of the specification describe the signs of infection used in a clinical setting, in contrast to the aspects of infection not presenting clinically. Further, Applicants submit that the arguments set forth above in connection with the discussion related to the phrase "protease associated with wound infection or ulcer formation" apply with equal relevance and force here. Applicants submit that the usage of the term is fully supported throughout the specification, and therefore, the term is not indefinite.

3. Claim 3 was rejected for use of the term "other factors". The term "factors" is exemplified on page 4 of the specification as "other proteases" present in the wound fluid, using language which mirrors the claim language. The term "other factors" is also used in context of a factor that can degrade a polymer as set forth in the specification. While not in agreement with the rejection, but in an attempt to advance prosecution, Applicants have amended claim 3 to use

the term "proteases" rather than "other factors". Accordingly, based on the use of the term in the specification, Applicants respectfully submit that the amended claims are not indefinite.

4. Claim 6 was rejected for recitation of the language "3 to 15" amino acids. Applicants submit that, based on the usage of this phrase in the specification, this phrase should clearly be understood to refer to a peptide of "3 to 15 amino acid residues in length". While not in agreement with the rejection, but in an attempt to advance prosecution, Applicants have amended claim 6 to more explicitly recite that the peptide is "3 to 15 amino acid residues in length". The use of the phrase in this context makes the meaning of the phrase unambiguous.

5. Finally, the term "substantially" was rejected as allegedly being indefinite. Applicants respectfully disagree. The term is used throughout the specification, and is exemplified in multiple instances (e.g., "substantially impervious", "substantially encapsulates"). The term "substantially" is permissible under well-established patent law, when exemplified as in the present application. For example, MPEP § 2173.05(b)(D) provides that the term "substantially" can be definite in view of general guidelines presented in the patent application. Such is the case with Applicants use of the term in the present application.

Nonetheless, while not in agreement with the rejection, but in an attempt to advance prosecution, Applicants have amended claim 18 to recite "substantially the whole area of the apertures in the apertured sheet is blocked." Applicants submit that the amended claim is not indefinite and request withdrawal of the rejection.

6. Claim 22 was rejected as allegedly indefinite for recitation of the phrase "at least one additional absorbent layer". Applicants have deleted the word "additional" to overcome the rejection. However, in response to the rejection, Applicants also note that despite the fact that claim 1 does not explicitly recite an "absorbent" layer, the claimed dressing does not exclude one or more absorbent layers and may encompass such.

Accordingly, because the presently-amended claims are not indefinite, Applicants respectfully request reconsideration and withdrawal of the rejections.

**Rejections under 35 U.S.C. § 112, First Paragraph ("Written Description")**

Claims 1-6, 13-16, 18, 19, and 22 were rejected as allegedly lacking written description. Applicants' best understanding of the Written Description rejection is that the rejection appears to be an assertion that the specification allegedly does not provide adequate written description for the following aspects of the claims: 1.) Proteases in the wound fluid; 2.) Matrix comprising polymers and a therapeutic agent; and 3.) Wound dressings and methods of making such dressings. Applicants respectfully disagree with all of the Written Description rejections set forth in the office action, and submit that the claims comply with 35 U.S.C. § 112, First Paragraph, for the following reasons.

Regarding the proteases in the wound fluid, Applicants submit that the response to the Indefiniteness rejection above applies with equal force in response to the Examiner's Written Description rejection. That is, Applicants have provided examples of wound fluids that may contain proteases that may be associated with wound infection. Nonetheless, in the interest of advancing prosecution of the application, Applicants have amended claim 1, from which the remaining rejected claims depend, to recite that the claimed proteases are selected from the group consisting of proteases that are elevated during infection and proteases that are elevated in wounds that are apparently not clinically infected but which go on to become infected within a few days. Furthermore, based in part on the description above, the specification provides the skilled artisan with abundant guidance as to how to determine a wound that is "not" apparently clinically infected, based on clear guidance as to what constitutes a clinically infected wound, and therefore, a wound that is apparently clinically infected.

Regarding the rejection of the matrix comprising a therapeutic agent, Applicants respectfully submit that the entire specification, and for example, pages 5 and 6, provides abundant support for a matrix comprising a therapeutic agent. Therefore, Applicants have provided more support that what is required by the corresponding patent laws. As provided in the case of *Falkner v. Inglis* (448 F.3d 1357, 1366 (Fed. Cir. 2006)), explicit examples are not necessary to support the adequacy of Written Description. As set forth previously, the incorporation of a therapeutic agent into a matrix such as those set forth in the present specification is something that is well known in the art. Indeed, MPEP § 2164.05(b) provides that "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public."

(Citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)).

Regarding the claimed wound dressings and methods of making the same, Applicants submit that the claims are supported by sufficient written description. In addition to the support identified above for the claims and the claim amendments, the entirety of the specification provides detailed descriptions of the compositions and methods of preparing such compositions. The specification provides abundant guidance to the skilled artisan as to how to make and use the claimed invention.

Accordingly, because all of the currently pending claims are supported by the required Written Description, Applicants respectfully request that the rejections be reconsidered and withdrawn.

**Rejections under 35 U.S.C. § 103(a)**

1. Claims 1, 3, 4, 6, 13-16, 18, 19 and 22 were rejected as allegedly being obvious over Peppas (Eur. J. Pharmaceutics and Biopharmacetics (2000) 50:27-46) and Suzuki (J. Biomed. Mater. Res. (1998) 42:112-116) and Arnold (EP Patent No. 0599589). The examiner argues that one of skill in the art would be motivated to combine hydrogel wound dressing taught by Pappas with the antibiotic-release wound dressings of Suzuki and the multi-layer wound dressings taught by Arnold. It is the Examiner's view that the combination of the cited patents would lead one of skill in the art to arrive at claims 1-4, 6, 13-16, 18, 19 and 22, in their entirety. Applicants respectfully traverse the Examiner's rejection for the following reasons.

The test which must be met for a reference or a combination of references to establish obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part, the proper test for obviousness:

> Office policy is to follow Graham v. John Deere Co. in the consideration and determination of obviousness under 35 U.S.C. § 103 ...
>
> [T]he four factual inquires enunciated therein as a background for determining obviousness are as follows:
>
> (A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;
(C) Resolving the level of ordinary skill in the pertinent art; and
(D) Evaluating evidence of secondary considerations. (MPEP § 2141).

When applying 35 U.S.C. § 103, the following tenets of patent law must be followed: 1) the claimed invention must be considered as a whole; 2) the references must be considered as a whole; 3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and 4) reasonable expectation of success is the standard with which obviousness is determined. MPEP § 2141 II. This test has not been satisfied here for any of the obviousness rejections.

It is clear that Suzuki teaches only the attachment of antibiotic, via chemical crosslinking of peptidyl moities, to a polymeric layer. The references do not provide any teaching or suggestion of the currently claimed pore structure, which releases therapeutic agent as the protease specifically cleaves oligopeptides to increase pore size.

In view of the amendments to the claims set forth herein, Applicants submit that the protease "associated" with the wound fluid in the present claims is not overly broad, and therefore, the use of this term as a basis for the obviousness rejection is unfounded. The protease associated with wound fluid, according to the amended claims, is a protease associated with a wound infection and with ulcer formation, and one which is elevated during infection and in wounds that are apparently not clinically infected but which go on to become infected within a few days. None of the cited references teaches this. Furthermore, none of the references teaches or suggests a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a protease associated with wound fluid such that the rate of release of the therapeutic agent increases in the presence of the protease. Therefore, there is nothing in any of the cited references or known in the art that would lead the skilled artisan to arrive at the presently-amended claims.

Consequently, because none of the rejected claims are obvious, as set forth above, Applicants respectfully request withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a). Further, applicants submit that claims 3, 4, 6, 13-16, 18, 19 and 22 are thereby allowable as written as depending from an allowable independent claim.

2. Claims 1, 3, 4, 6, 13-16, 18, 19 and 22 were rejected as allegedly being obvious over Peppas, Suzuki, and Arnold, further in view of Ulbrich et al. (Journal of Controlled Release

2000, 64:63-70). Applicants respectfully traverse the Examiner's rejection for the following reasons.

As a preliminary matter, claim 2 has been cancelled, rendering moot the rejection of this claim.

The Office Action states that the teaching of N-(2-hydroxypropyl)methacrylamide (HPMA) by Ulbrich further makes the claimed invention obvious to one of skill in the art. Applicants submit that Ulbrich's teaching in no way makes up for the deficiencies of Peppas, Suzuki, and Arnold, as set forth above, and therefore, that nothing about the combination of Peppas, Suzuki, Arnold, and Ulbrich would make the amended claims obvious, because Ulbrich does not provide any teaching or suggestion that the protease associated with wound fluid, according to the amended claims, is a protease associated with a wound infection and with ulcer formation and one which is elevated during infection and in wounds that are apparently not clinically infected but which go on to become infected within a few days, and furthermore, Ulbrich does not provide any teaching or suggestion that a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a protease associated with wound fluid such that the rate of release of the therapeutic agent increases in the presence of the protease. Therefore, there is nothing in any of the cited references or known in the art that would lead the skilled artisan to arrive at the presently-amended claims.

Consequently, because none of the rejected claims are obvious in view of Peppas, Suzuki, Arnold, and Ulbrich, as set forth above, Applicants respectfully request withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a). Further, applicants submit that claims 3, 4, 6, 13-16, 18, 19 and 22 are thereby allowable as written as depending from an allowable independent claim.

3. Claims 1, 3-6, 11, 13-16, 18, 19 and 22 were rejected based on a combination of Peppas, Suzuki, Arnold, and Ulbrich, further in view of Pachence (WO00/64486). Applicants respectfully traverse the Examiner's rejection for the following reasons.

As a preliminary matter, claim 2 has been cancelled, rendering moot the rejection of this claim.

The Office Action states that the teaching of peptide linkers by Pachence further makes the claimed invention obvious to one of skill in the art. Applicants submit that Pachence's

teaching in no way makes up for the existing deficiencies of Peppas, Suzuki, Arnold, and Ulbrich as set forth above, and therefore, that nothing about the combination of Peppas, Suzuki, Arnold, Ulbrich, and Pachence would make the amended claims obvious, because Pachence does not provide any teaching or suggestion that the protease associated with wound fluid, according to the amended claims, is a protease associated with a wound infection and with ulcer formation and one which is elevated during infection and in wounds that are apparently not clinically infected but which go on to become infected within a few days, and furthermore, Pachence does not provide any teaching or suggestion that a matrix comprising polymers joined by cross-linkages which cross-linkages comprise oligopeptidic sequences which are cleavable by a protease associated with wound fluid such that the rate of release of the therapeutic agent increases in the presence of the protease. Therefore, there is nothing in any of the cited references or known in the art that would lead the skilled artisan to arrive at the presently-amended claims.

Consequently, because none of the rejected claims are obvious in view of Peppas, Suzuki, Arnold, Ulbrich, and Pachence as set forth above, Applicants respectfully request withdrawal of the rejection of claim 1 under 35 U.S.C. § 103(a). Further, applicants submit that claims 3-6, 13-16, 18, 19 and 22 are thereby allowable as written as depending from an allowable independent claim.

**Double Patenting Rejection**

Claims 1, 3-6, 11, 13-16, 18, 19 and 22 were rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-4 and 7-16 of copending Application No. 12/041,955 in view of Arnold. Applicants disagree with the grounds for rejection, and furthermore, submit that the claims are not obvious in view of the amendments made herein. However, at this time, Applicants respectfully request that the double patenting rejection be held in abeyance until claims in either this or the copending application are deemed to be allowable. At the time claims from one of the applications are found to be allowable, Applicants will consider the Examiner's rejection in view the final version of the allowable claims.

**Conclusion**

Applicants respectfully submit that the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 963-5809 to clarify any unresolved issues raised by this response.

The Director is hereby authorized to charge/credit Deposit Account No. **50-0310** (Billing No. 088888-0105) for any other required fees, deficiencies or overpayments in connection with this Response.

Respectfully submitted,

**PATRICK TROTTER ET AL.**

Date: August 12, 2010

By: /Thomas M. Sossong Jr./

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